REMARKS

The Examiner's indication that claims 16-21 would be allowable in independent form has been noted with appreciation.

Better copies of the drawings are submitted herewith.

The statement of preference in the claims has been deleted and restated in separate dependent claims. The scope of the claims being amended in this way has not been narrowed. As a result, it is respectfully submitted that the rejection of various claims on this basis under 35 U.S.C. 112 can now be withdrawn.

The non-statutory claims 35 and 37 have been cancelled.

Some minor grammar changes have been made without changing the scope of the claims.

Claim 15 has been amended for consistency with claim 1.

Claims 1-13 and 15 were rejected under 35 U.S.C. §103 over Ferruti; claims 1, 15 , 22 and 31 and the claims dependent thereon over Erout; claims 1, 15 and the claims dependent thereon over Shah; claims 1, 15 and claims dependent thereon over Yu and claims 1, 22, 31 and claims dependent thereon over Cole or Yang. All of these rejections are respectfully traversed.

The independent claims, and thereby all of the claims rejected, call for the polymer to have a polydispersity of less than 1.4. Since the failure of the prior art to teach or suggest this feature of the invention is sufficient to cause the rejections to be untenable, the following discussion will be limited to a discussion of this point. It is

unnecessary to discuss other differences between the cited art and the claimed invention.

It was well known to prepare precursor polymers containing active acyl groups which were capable of conjugating covalently to biologically active molecules. A detailed review of the prior art is included within the text of the present application and the Examiner has cited a number of documents further illustrating this fact. However, it had not proved possible to prepare precursor polymers with a reliable, reproducible structure that had a narrow molecular weight distribution prior to the date of the present invention. Accordingly, it had not proven to be possible to use such narrow molecular weight distribution precursor polymers to prepare functionalized polymers with a narrow molecular weight distribution and, therefore, reliable, reproducible properties. The narrow molecular weight distribution precursor polymers of the present invention, acknowledged in the Office Action to be new, can be utilized to prepare narrow molecular weight distribution, polyfunctionalized polymers that also have never been made before and which, moreover, cannot be prepared by known polymerization processes. The ability to use narrow molecular weight functionalized polymers is particularly important for medical applications, especially those which require parenteral administration or uptake into the circulatory or lymphatic system. It is known that broader molecular weight distribution polymers display a wider range of toxic effects.

In addition to the application to make functionalized polymers for drug delivery, the narrow molecular weight distribution precursor polymers of the present invention can also be utilized in pre-clinical development to generate libraries of functionalized homopolymers and co-polymers from the same precursor polymer, at a particular molecular weight. This realizes the preparation of candidate functional polymers which have the same narrow molecular weight characteristics but differ only

in chemical functionality. It allows the art a mechanism in which different ligands can be compared using a particular molecular weight polymer with a narrow dispersity. As a result, changing the chemical functionality can be compared while keeping the molecular weight constant and at the same time maintaining a narrow molecular weight distribution. It is not possible to achieve this effect with other methods.

Prior to the present invention, it was not known how to make precursor polymers with a narrow molecular weight distribution. It had not been possible to effectively control the molecular weight, which was usually very high with a broad molecular weight distribution, because the nature of monomers typically result in highly exothermic and uncontrolled polymerization. None of the art advanced against claims in this application teach or suggest a polymer having a polydispersity of less than 1.4, and preferably less than 1.2. Indeed, with one exception, the prior art does not even consider polydispersability.

Ferruti (which is referred to in most of the other prior art cited) is concerned with prostaglandin-containing polymers and contain no mention of the significance of a low molecular weight distribution, nor does the reference have any disclosure of a method of making a polymer having a low molecular weight distribution. Ferruti has no indication that molecular weight is of any significance and there is no mention of molecular weight or molecular weight distribution for any of the polymers that are prepared.

Erout concerns copolymerization of N-vinyl pyrrolidone and N-acryloxy succinimide, and discusses the kinetics of the reaction. However, there is no discussion about the production of narrow molecular weight distribution polymers derived from the monomers.

Shah concerns copolymers of N-isopropyl acrylamide and N-acryloxy succinimide prepared either by radical polymerization of the monomers or by reaction of isopropylamine with poly(N-acryloxy succinimide). The object of this study was to improve the kinetic profile of drug release based on the water content of the polymer. There is nothing in this reference which mentions the importance of molecular weight distribution or contains any suggestion on how to control it.

Yu is concerned with radiation-induced solid state polymerization of acrylic and methacrylic esters of N-hydroxysuccinimide and N-methacryloxysuccinimide. Once again there is nothing which mentions the importance of molecular weight distribution of how to control it. This reference is particularly concerned with polymerization yield rather than molecular weight or the molecular weight characteristics of the polymers produced.

Cole describes the polymerization of N-isopropyacrylamide to form poly(N-isopropylacrylamine), which is a reaction quit different from that other invention. Once again, there is no mention of molecular weight distribution or its importance.

The Yang reference is the only piece of prior art which makes any reference to polydispersity and that reference does not lead one to the present invention. Table II of Yang shows that polydispersity ($M_w \backslash M_n$) of the polymers which were made and the Examiner will note that the polydispersity is high with all of the polymers having a polydispersity of 1.5 or greater. The Examiner will also note that the objective of Yang was to control the ligand frequency along the polymer chain and this was achieved by controlling various parameters of the reaction. The reference discusses how various parameters effect ligand frequency and molecular weight but contains no discussion about the effect of polydispersity. Yang does summarize:

> We have found that the molecular weight of the active ester copolymer . . . increases with the increase in the ratio of toluene to THF while the average ester content of the activated polymer is almost invariant with change of this ratio. These results suggest that it is possible to control the average number of active groups per polymer chain by adjustment of the comonomer feed ratio along with the composition of the solvent system used for polymerization.

This indicates nothing about polydispersity. There is nothing in the reference as to how polymers can be prepared in which only the chemical identity of the ligand is changed, without also changing the molecular weight. This is not possible to achieve by the process described by Yang. In contrast, the present invention provides a mechanism by which the effect of changing a ligand and polymer can be studied without complications caused by varying molecular weight to give a narrow weight distribution functionalized polymer.

In none of the prior art advanced in the rejections is the desirability to control the polydispersity considered and there is no suggestion as to how polydispersity could or should be controlled. Because of this common deficiency, it is respectfully submitted that all of the rejections based on the prior art should be withdrawn.

The Examiner is respectfully advised that an IDS is being submitted simultaneously with this Amendment. It includes two (2) articles which make reference to molecular weight distribution of polymers. One is a paper by Mammen which contains the sentence "the distribution of molecular weight was narrow" (second column following Fig. 3, page 4182), but the experimental section on page 4189 makes it clear that the distribution was actually 1.9. A paper by Choi states "further purification and fractionation may be necessary to achieve an active polymer with a narrow molecular weight distribution" in the second column of page 4104. The authors did not obtain or try to obtain a polymer as specified in the instant claims which has a narrow, specified molecular weight distribution and molecular weight. Purification as

envisioned in this article is tedious and difficult to reproduce. Fractionation is low yielding, not used on a commercial scale and does not provide a means for control of molecular weight in that it only allows for narrowing the molecular weight distribution with molecular weight itself being controlled by polymerization conditions. Applicants believe that neither of these references negate the patentability of the instant invention but the Examiner is respectfully requested to review the articles and consider their disclosure when evaluating this response.

In light of all of the foregoing it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited.

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Respectfully submitted,

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